Meta-Analysis of PET and SPECT Imaging Studies of Adult Age Differences in the Dopamine System

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Background

The normal aging process is accompanied by behavioral performance declines in various cognitive functions, e.g. working memory[1], processing speed[2], and attention regulation[3]. Theories suggest that this impairment is related to decline of the dopaminergic system[4] across adulthood, since these functions have been associated with the neurotransmitter dopamine (DA). Over the past 30 years many studies have used positron emission and single-photon emission computed tomography (PET and SPECT, respectively) to assess adult age differences in the DA system.

Both methods enable us to study neurotransmitter functionality by in-vivo radioligand imaging: the administered radioligand binds with high affinity to a specific receptor, transporter or presynaptic vesicle. Tracking the decay of the tagged radioactive isotope allows for the determination of the location, binding affinity, and density of the target receptor or transporter in the regions of interest in the brain[7]. Due to intense costs of these techniques and consequently low sample sizes, most studies lack power and therefore convincing results.

Selective, qualitative summaries of the SPECT and PET imaging literature[5,6] have described a strong negative relationship between age and dopamine function overall, but there are often overlooked inconsistencies in the size of the effects. The goal of this study was to perform a systematic meta-analysis of SPECT and PET studies examining adult age differences in dopamine synthesis capacity, receptors, and transporters to yield quantitative measures of average effect sizes. Additionally, we examined potential moderators which might account for heterogeneity across studies.

Methods

LITERATURE SEARCH. U.S. National Library of Medicine's Medical Subject Heading (MeSH) terms associated with an initial set of papers (n=42) were combined for a broad search for additional papers in the PubMed database, for example:

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"Humans"[Mesh] AND ("Aging"[Mesh] OR "Aged"[Mesh]) AND "Tomography,
     Emission-Computed"[Mesh] AND "Receptors, Dopamine"[Mesh]
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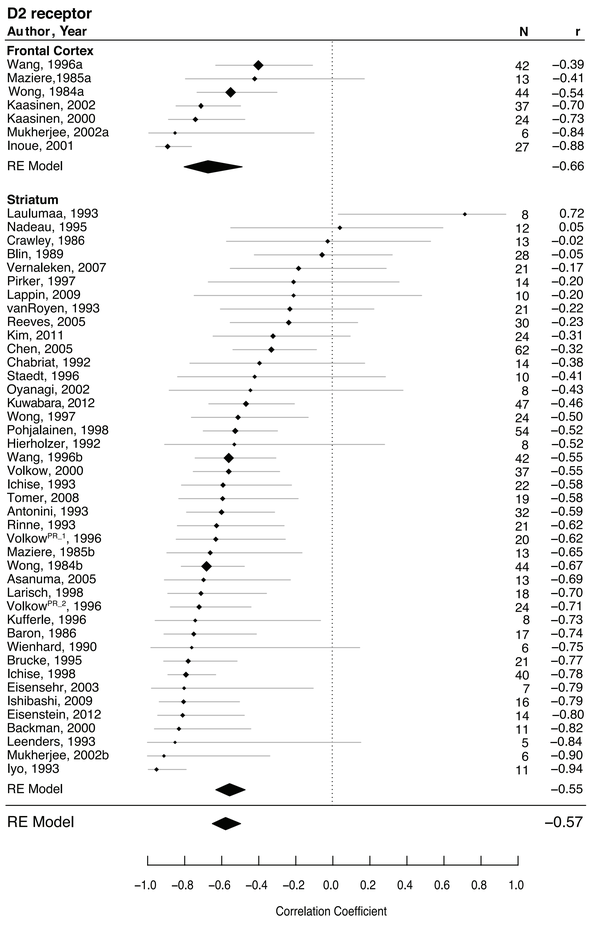
The resulting corpus (n = 573) was the basis for selecting studies that met our inclusion criteria (N = 88):

1. Studies reporting original results, published in a journal accessible through Yale University's library system;
2. Studies reporting data from a sample of healthy, human adults (> 18 years) with a minimum age range of 25 years;
3. Studies reporting either a linear correlation between age and a dopamine-relevant kinetic measure from emission computer tomography or data comparing dopamine-relevant kinetic measures in separate age groups.

DATA EXTRACTION. The linear correlation coefficients between age and the PET or SPECT kinetic measure used to assess neurotransmission were obtained a) directly from a report in the study, b) from single subject data provided in a table or a graph, or c) from reported group values of young and old adults which had to be transformed into Cohen's d first.

DATA ANALYSIS. Using the `metafor` package[8] in R (v. 3.3.2) we applied separate random-effect meta-analyses for each marker to obtain summary correlation coefficients over the included estimates weighted by their sample sizes. To determine the source of potential heterogeneity between studies we applied a meta-regression. Additionally, for a subset of the studies we calculated a sample size weighted average for each marker to quantify how much the different dopamine markers change per decade.

Results



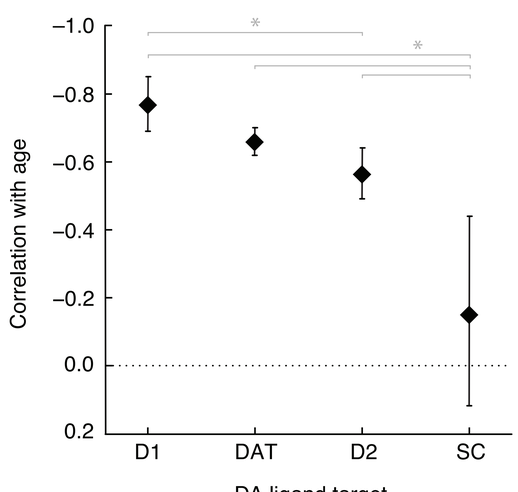
Positions of diamond on the x-axis represent effect size of each included study with values and sample size listed to the right. Grey bars indicate the 95% confidence interval (CI) of the study's effect size. Polygons represent mean standardized correlation coefficient (random effects meta-analysis) and 95% CI.

Age differences in the dopamine system

marker	% change per decade *	r	studies	subjects
D1	**-12.4**	**-0.79**	**4**	**88**
D1 frontal Cortex	-14.1	-0.76	4	70
D1 Striatum	-11.1	-0.81	3	88
DAT	**-8.8**	**-0.68**	**30**	**873**
D2	**-8.4**	**-0.57**	**44**	**963**
D2 frontal Cortex	-9.3	-0.66	7	193
D2 Striatum	-8.2	-0.55	41	875
DAP	**-4.9**	**-0.15**	**13**	**257**
DAP Midbrain	-9.3	-0.2	3	70
DAP frontal Cortex	-10.8	-0.57	3	64
DAP Striatum	-2.8	-0.16	12	236

The table summarizes meta-analytic results.
* A subset of 76 studies were used in % change per decade calculations.

Comparison of age differences in DA marker



The figure compares the average correlation with age (represented by diamonds) as well as their 95% CI in different dopamine ligand targets. The dotted line indicates an age effect of zero.

Discussion

CONCLUSIONS. Our meta-analytic results provide robust evidence (across 88 studies and 2,149 subjects) for an age-related decline in DA receptors as well as DA transporters. The average correlation with age was significantly more negative for D1-like compared to D2-like receptors. In the light of the two-state model of DA in the prefrontal cortex by Seamans and Yang (2004)[9], a possible implication of steeper decline in D1 compared to D2 with age is that individuals may be more likely to be in a D2- rather than D1-dominated brain states as they age. This is consistent with evidence that older adults have more difficulty with selective attention[3] which could affect memory[1] and decision making[10]. In contrast, we did not find an association between age and DA synthesis capacity. This suggests that older adults maintain a similar potential to produce DA in the presynaptic cell as younger adults. This relative sparing within the DA system (combined with steep declines in transporters) reveals a possible mechanism that may explain minimized or eliminated age differences in cognitive functions when using stimuli that are more personally salient for older adults (e.g., goal-relevant or socioemotional stimuli)[11-14].

LIMITATIONS. Most studies did not correct for partial volume effects which could have lead to overestimation of the age effect especially if the scanner resolution was low. Furthermore, we were not able to assess the link between age-related changes of the DA system and cognitive decline in age since the few studies reporting this were examining very heterogeneous cognitive measures.

FUTURE DIRECTIONS. Future studies can test our hypothesis regarding larger age differences in D1- versus D2-state related processes. Very few cognitive aging studies directly assess DA function and those that do most often assess receptors. The present meta-analytic results suggest that more research should be done examining the reliability and potential consequences of relatively reduced age-related decline in synthesis capacity.

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